

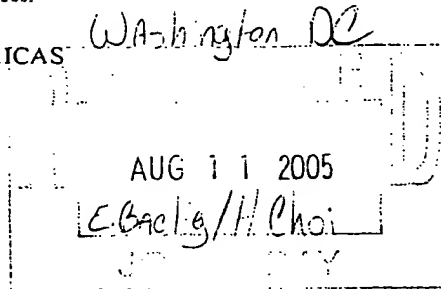


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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/447,218	11/23/1999	A.K. GUNNAR ABERG	4821-362	3537

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PENNIE & EDMONDS LLP
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NEW YORK, NY 10036



EXAMINER

CRANE, LAWRENCE E

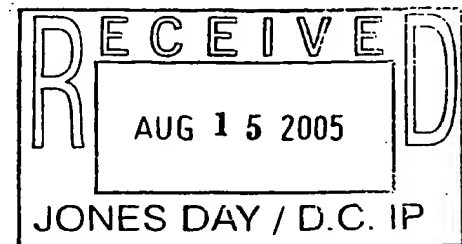
ART UNIT PAPER NUMBER

1623

DATE MAILED: 08/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Amendment Due 11/1/05 (SL)
Appeal Due 1/4/06 (SL)



Office Action Summary

Application No.

09/447,218

Applicant(s)

ABERG ET AL.

Examiner

L. E. Crane

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on May 18, 2005 (amdt).
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 34, 36, 38-40 and 50 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 34, 36, 38-40 and 50 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 5/18 & 6/15/2005.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Claims 1-33, 35, 37 and 41-49 have been cancelled, no claims have been amended, the disclosure has not been amended, and new claim 50 has been added as per the response filed May 18, 2005. Two additional Information Disclosure Statements (2 IDSs) filed May 18, 2005 and June 15, 2005 have been received with all cited references. A declaration signed by William W. Storms, M.D. has also been received with Exhibits A, C and D complete, but with the documents listed on Exhibit B not all bibliographically complete. Documents listed in Exhibits B and D which are bibliographically complete have been cited on the attached PTO-892. But, references E-6, E-9, E-10, E-11 (No dates of publication, some author and publisher information incomplete) could not be made of record because these references did not have complete bibliographic information included for same on either the face of the document or in the listing of references provided by applicant or both. Resubmission is respectfully requested together with the missing bibliographic information preferably printed on a PTO-1449.

Claims 34, 36, 38-40 and 50 remain in the case.

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

"A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made."

Claims 34, 36, 38-40 and 50 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Berkow et al.** (PTO-892 ref. R) in view of **Villani et al.** '716 (PTO-1449 ref. AE).

The instant claims are directed to the treatment of urticaria (aka hives, a condition associated with allergic reactions) by the administration of an effective dosage of descarboethoxyloratadine (DCL) to a patient in need thereof. The dosage is further defined as 0.1 mg to less than about 10 mg per day or less than about 5 mg per day. Claim 36 further limits claim 34 by limiting the population of hosts to those "... humans with a higher than normal propensity for or incidence of cancer."

Berkow et al. discloses at p. 333, beginning in the third line under "**Treatment**," that "[s]ymptoms [of urticaria] usually can be relieved with an oral [dose of an] antihistamine"

Villani et al. '716 discloses at column 1, lines 39-46 that descarboethoxyloratadine (DCL) and closely related compounds are effective antihistamines with the advantage of low CNS-related side effects, i.e. that DCL and relatives are non-sedative. Villani also discloses at column 8, lines 11-46 that the dosage range is about 1 mg to 40 mg for a 24 hour period and preferably from about 5 to about 10 mg over this time period (column 8, line 19). More generally the unit dosage is defined as "from 1 mg to 1000 mg according to the particular application" (column 8, lines 43-44).

The findings that

- i) Villani et al.'s teaching that DCL and related compounds are known to be effective antihistamines,
- ii) the teaching by applicant that DCL has the expected effect in the treatment of urticaria (hives) as predicted by Berkow et al.,
- iii) the teaching of dosages ranges which overlap with the claimed dosage ranges, and
- iv) the failure of applicant to establish statistically significant unexpected results (no error analysis of the data provided),

when taken together with the disclosure of Berkow et al. are deemed to establish that combination of the instant combination of references is properly motivated. These particular disclosures are also deemed to render the instant claimed subject matter lacking in any patentable distinction in view of the noted prior art.

Therefore, the instant claims directed to treatment of urticaria by the administration of the antihistamine DCL, including within the dosage ranges of the instant dependent claims, would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments filed May 18, 2005 have been fully considered but they are not deemed to be persuasive.

Applicant argues that in Berkow is not applicable because only first generation antihistamines are listed as examples and furthermore that the prior art teaches that not all antihistaminic agents can be used to treat urticaria. After noting examiner's counter argument that even Berkow acknowledges that not all antihistamines are effective in every patient, applicant further argues that the instant claims are "not obvious because Berkow does not

disclose the use of DCL for the treatment of urticaria, and does not even suggest that all antihistaminic agents are effective in treating urticaria.” (emphasis in original) Examiner respectfully disagrees with applicant’s conclusion that “... Examiner is in complete agreement with Applicant that Berkow does not render obvious the treatment of urticaria with all known antihistamines.” (emphasis in original) Applicant then concludes without more that Berkow is “... nothing more than an invitation to experiment,” without even considering the contents of the other primary reference. Applicant then leaps to the conclusion that because “... an invitation to experiment is not a proper basis for an obviousness rejection, ... the rejection ... should be withdrawn.” Examiner respectfully disagrees with this line of reasoning for the following reasons. First, the standard for obviousness does not require that a single reference must meet the standard for anticipation, i.e. that all elements of a rejection over prior art must be present in a single reference. Second, applicant alleges that the Berkow reference fails because it must teach the specific active ingredient specified by the instant claims. Again this is the standard for anticipation, not the obviousness standard.

Applicant then argues beginning in the first full paragraph of page 6 of the response that Villani does not remedy the deficiencies of Berkow. Applicant then cites at length portion of the Storm declaration to the effect that the side effects attributed by Dr. Storm to DCL were so serious that no one would have considered DCL to be a proper candidate for use as an antihistamine for the treatment of urticaria as of the earliest priority document filing date in 1994. Examiner respectfully disagrees for the following reasons. Looking first at the paragraphs 12-15 of the Storm declaration, examiner notes that applicant’s arguments are based on Dr. Storm’s explanation of the standards applied to Food and Drug Administration (FDA) proceedings concerning the process of obtaining US government permission to market a pharmaceutical. In particular examiner notes that in paragraph 14, Storm states that “... I considered reports concerning the adverse effects of one [piperidine] H₁ antagonist to be relevant to the safety of other members of that class.” While examiner commends Dr. Storm for his extensive experience in FDA proceeding as documented in his lengthy resume, examiner does not agree that what appears to be a “safe and effective” analysis applies in this forum (before the USPTO); patentability, except where there is clear evidence of inoperability, is an entirely different determination. Applicant’s have cited paragraph 17 of the instant declaration, a paragraph which appears to represent the professional opinion of Dr. Storm, but is presented without any data whatsoever to support his allegation that “cardio-toxicity,”

"personality changes" and "tumour growth" are associated with the administration of any level of dosage of DCL. Examiner has carefully reviewed the extensive list of references submitted by Dr. Storm and finds that no combination of these references can provide an adequate factual basis for concluding that DCL is inoperable as an antihistamine. Again examiner emphasizes that the standard for inoperability under 35 U.S.C. §101 is entirely different than those standards applied by the FDA in their proceedings.

Applicant concludes by arguing that the Berkow and Villani references are not properly applied under the statute and therefore that the rejection should be withdrawn. Examiner respectfully disagrees. The rejection has been maintained because the references cited teach generally that antihistamines are useful in the treatment of urticaria (Berkow) and that claims 3 and 15 of Villani '716 are directed specifically to the treatment of "allergic reactions," where the quoted term is, according to at least one medical dictionary, a synonym for the term "urticaria."

Examiner has reviewed in detail the declaration of Dr. William Storm. Dr. Storm is clearly knowledgeable in the medicinal antihistamine art, but the instant declaration appears to be beside the point. The instant declaration is of record in an application at the U. S. Patent and Trademark Office (USPTO), not the Food and Drug Administration (FDA). The USPTO is concerned with the disclosure and patenting of inventions, but the USPTO is not in the business of giving permission to market drugs (an FDA matter as suggested by the "safe and effective" language in declaration paragraph 22). Therefore, while Dr. Storm's concerns about side effects would probably be relevant to proceeding before the FDA as suggested by paragraphs 18 and 21 of the instant declaration, these concerns are not relevant to proceedings before the USPTO unless there is a factual disclosure (i.e. a substantial body of relevant test data) that the side effects are real (extrapolation of tests of other compounds, opinions and/or speculations are not enough), that said side effects are actually caused by the pharmaceutical in question, and that said side effects render the pharmaceutical in question completely unable to have the beneficial effect described in a patent claim (i.e. that the invention being claimed is inoperative under 35 U.S.C. §101). Because the instant declaration has not provided an adequate basis to support the conclusion that the prior art (Villani and Berkow) are (or were) inoperative, the instant declaration does not provide a disclosure which is sufficient to support a conclusion that the instant claims are patentable in view of said prior art; i.e. this declaration does not provide an adequate factual basis for disqualification of the cited prior art. Therefore,

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examiner concludes that the instant declaration for the most part is not relevant to the question of patentability in the instant case.

Claims 34, 36, 38-40 and 50 are rejected under 35 U.S.C. §103(a) as being unpatentable over Swinyard (II) (PTO-892 ref. TA) and Swinyard (I) (PTO-892 ref. SA) in view of Villani et al. '716 (PTO-1449 ref. AE) and further in view of Brandes et al. (PTO-892 ref. RA).

The instant claims are directed to the treatment of urticaria (aka hives) by the administration of an effective dosage of descarboethoxyloratadine (DCL) to a patient in need thereof and avoidance of the side effects thereof. The dosage is further defined as 0.1 mg to less than about 10 mg per day or less than about 5 mg per day.

Swinyard (II) discloses the utility of H₁-antihistamines in the treatment of urticaria at page 1124, column 1, line 4 of the third paragraph following the heading "Antihistamines." And at page 1130, column 2, this reference discloses the antihistamine azatadine maleate which is a very close structural relative of both loratadine and descarbethoxyloratadine (DCL), sharing with both the identical four ring molecular skeleton and similar antihistamine activity.

Swinyard (I) discloses at pages 778-782 (see page 779, paragraph beginning at column 1) that only certain H₂-antihistamines cause problems with liver P450 enzyme metabolism, but that selection of an alternative H₂-antihistamine is an effective way to avoid this difficulty.

Villani et al. '716 discloses at column 1, lines 39-46 that descarboethoxyloratadine (DCL) and closely related compounds are effective antihistamines with the advantage of low CNS-related side effects, i.e. that DCL and relatives are non-sedative. Villani also discloses at column 8, lines 11-46 that the dosage range is about 1 mg to 40 mg for a 24 hour period and preferably from about 5 to about 10 mg over this time period (column 8, line 19). More generally the unit dosage is defined as "from 1 mg to 1000 mg according to the particular application" (column 8, lines 43-44).

Brandes et al. discloses in the last sentence prior to the "CONCLUSION" that loratadine promotes the growth of two well known neoplasms. This issue is addressed by the instant disclosure at page 24, lines 20-25, with data which is at best incomplete because only one

comparison is made and because there is no statistical error analysis permitting determination of whether the difference suggested by the data is statistically significant.

The motivation to combine the above references is that each is directed to positive and/or negative effects observed following the administration of antihistamines. The primary reference, Swinyard (II) clearly is well motivated in combinations with the remaining references, because this reference discloses all of the side effects commonly associated with H₁-antihistamine administration, and how these may be avoided by substitution of alternative antihistamines, including an antihistamine which is a close structural relative of both loratadine and DCL.

The substitution of DCL for loratadine or its analogue azatadine is deemed to have been an obvious substitution of the ordinary practitioner seeking to optimize the treatment of urticaria as reported in Swinyard (II) in view of the disclosure of Villani et al. that DCL is, like loratadine, also an antihistamine. The additional guidance provided by the Swinyard (I) and Brandes references merely adds to the already extensive discussion in Swinyard (II) of the side effects observed following administration of medicinally appropriate dosages of numerous antihistamines, and therefore would have afforded the ordinary practitioner more than sufficient guidance to make an appropriate determination of whether or not to use DCL to treat urticaria in a given human host in need thereof. These particular disclosures are also deemed to render the instant claimed subject matter lacking in any patentable distinction in view of the noted combination of prior art.

Therefore, the instant claims directed to treatment of urticaria by the administration of the antihistamine DCL when appropriate in light of possible side effects, including within the dosage ranges of the instant dependent claims, would have been obvious to one of ordinary skill in the art having the above cited references before him at the time the invention was made.

Applicant's arguments filed May 18, 2005 have been fully considered but they are not deemed to be persuasive.

Beginning at the bottom of page 7 of the instant response applicant argues that Swinyard (II) is an inappropriate reference because "... while 'enormous number [sic] of clinical conditions for which antihistamine drugs have been suggested,' these drugs 'vary from *effective* to *ineffective* in these conditions,' this [reference] clearly teaches that no